Message

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Sent: 12/20/2019 4:09:29 PM
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Subject: RE: Chloroprene PBPK: in vitro data / parameters

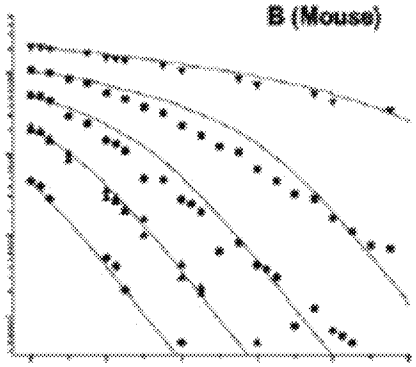
Wrapping up the QA (in vitro data and modeling):

I've created over-lay plots of the figures from Himmelstein et al. (2004) and Yang et al. (2012). I also checked the numbers in the data arrays from the model – those in the 'data' scripts – against those in the 'Graphs in vitro rodent.xlsx' Excel file. For the later I didn't check every single value, but over 20% of the values, as specified in the QAPP. There were no apparent discrepancies between the Excel file and the data scripts, and no discrepancies between plots of those data and the points in Yang et al. (2012) (copied images).

I do note that in the IISRP in vitro report, which contains original data for each incubation (new data reported by Yang et al. (2012)), there are some cases where repeat incubations were conducted. For example, there is a repeat of the 1 ppm incubation for the female mouse lung. Looking at those two incubations in particular, the data used in the analysis and shown in the plots are average values for the two incubations, which makes sense if one only seeks to evaluate mean values of the parameters. I have not looked at every set of results in the report, but from my scan it seems that within each species/gender/tissue set of incubations (e.g., male mouse kidney) there is at most one incubation concentration where the incubation is repeated. For the majority of the data only a single incubation is run for each concentration. Given the number of concentrations evaluated, there is certainly information on vial-vial variability in the data, but that requires a higher level of analysis such as MCMC to quantify. Because the plots only show means of repeated incubations, the extent of this variability can't be seen in those plots.

In contrast, the experiments in Himmelstein et al. (2004) used staggered start times and one can tell from looking at the plots that there's some variability between vials. An example is just below. While the original data tables are not available, one could reconstruct the results for each vial on the assumption that the sampling interval is fairly consistent at 0.2 h. As stated previously, I believe doing this will be necessary to fully evaluate the uncertainty in the human population-mean parameters, but we can wait for the peer review panel to pass judgment on that, if that is how Ramboll and Denka wish to proceed.

Male mouse liver oxidation data from Himmelstein et al. (2004)



For the male mouse liver and lung, there are discrepancies between the numerical data and the figures that are likely not an artifact of digitizing the data (assuming the data were recovered from the published figures this way). Plots are copied at the bottom of this email. There are a couple of points where the sample time is wrong and a number where it appears that an average value is used to replace multiple points at the same time. For these tissues where metabolism is significantly faster than control losses, the differences likely have little impact on estimate parameter mean values, but to conduct an analysis which treats each incubation vial as the experimental unit, and fully evaluate parameter uncertainty, these data should be re-digitized.

Since the human lung data show only a single point at each sampling interval, and Himmelstein et al. (2004) otherwise appears to have plotted each measurement separately (rather than mean values), I conclude that only one incubation was conducted at each exposure level for the human lung (1 vial/concentration).

As a part of revising the charge questions, and background info for that, I plan to create a plot showing the variability in background losses from those data vs. the range predicted from the statistical sample in ControlData.m (in the CDMCMC project). I understand this numerical array to be a sample of the posterior distribution for the 'population' mean loss rate (log-transformed), which was then used when estimating metabolic parameters. Here, 'population' means the population of incubation vials from which data are obtained. I plan to use that to create a 'cloud' of predicted losses for a 1-hour incubation and compare that to the range among the incubation vials in a plot. The data will be normalized to the initial value in each set, to illustrate the range in loss rate, separate from variability in initial value. Based on my previous, more rapid comparison, I believe that the simulated range will be much less than the observed range. It is already clear that the extent to which human lung metabolism exceeds the mean loss rate is quite small, but that this result is very sensitive to the assumed loss rate. The *uncertainty* in the human lung metabolism is therefore dependent on the uncertainty in the loss rate (vial-to-vial variability), which appears to be under-represented in this analysis. Based on my analysis, a rigorous upper bound on the human lung metabolism (i.e., a rigorous 95% confidence upper bound on the mean rate of metabolism in this mixed tissue sample) may be considerably higher than either the upper bound indicated from the MCMC analysis presented and the alternate value estimated from a marker substrate proposed as an alternative (results shown in previous email).

I suggest EPA should quantitatively evaluate the impact of that uncertainty in any subsequent application of the PBPK model for risk assessment which depends strongly on the estimated human lung metabolism. Hence it really should be rigorously evaluated in the in vitro metabolic analysis. I say this to emphasize my conclusion that the uncertainty bounds from the MCMC analysis should be included in the report and a full description of the statistical model and underlying assumptions, to allow the external reviewers to fully evaluate these.

Sincerely,
-Paul
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Male mouse liver data QA
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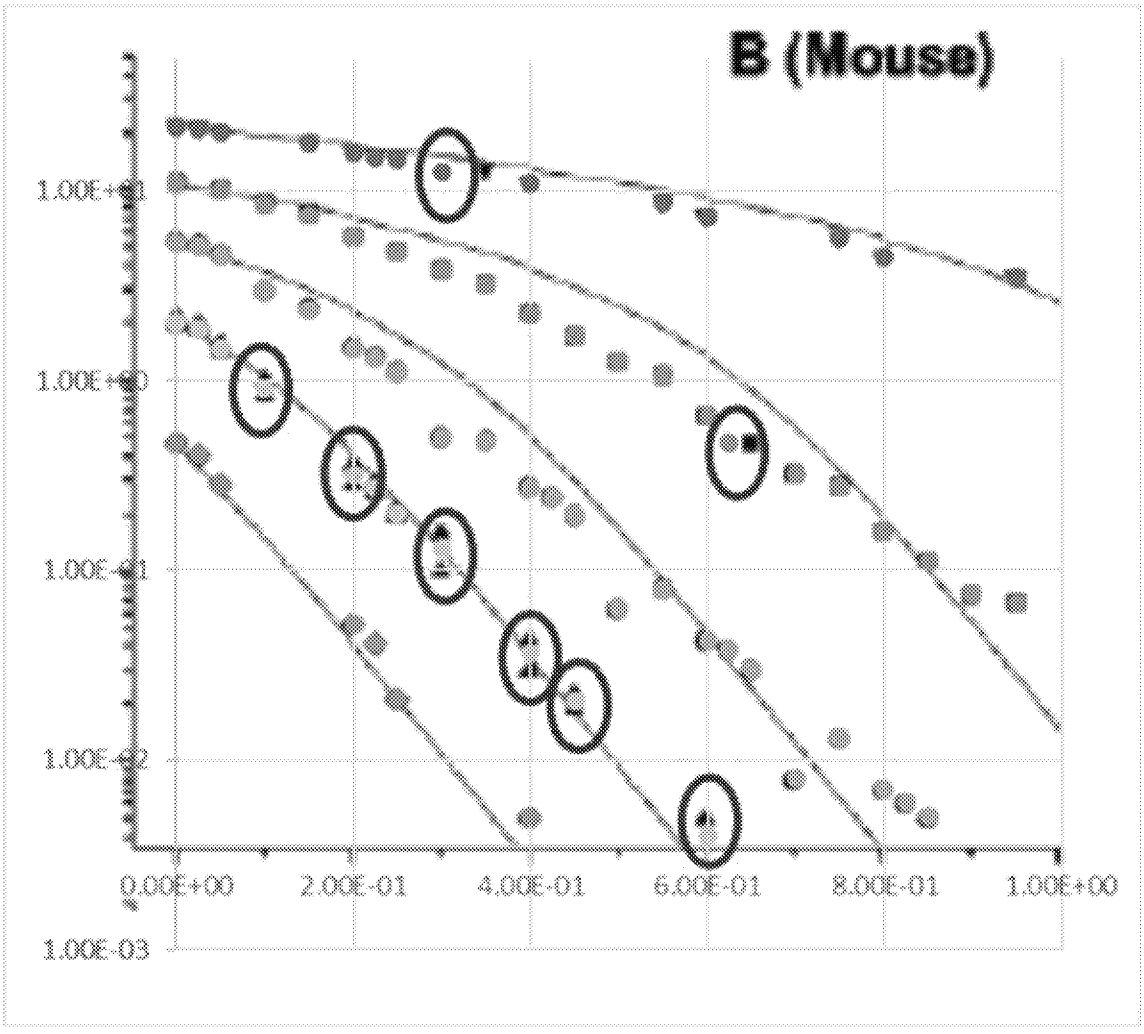

Male mouse lung data QA